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HEREDITARY ŒDEMA.

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ALTHOUGH the influence of heredity as a factor in the production of certain forms of œdema, not of cardiac or renal origin, was mentioned by Quincke in 1882, it was not until 1888, when Osler published the details of a case, that the subject attracted general notice in this country. This was probably due, first, to the eminent position held by the latter writer in the medical world, and, second, to the exceptionally favorable circumstances that enabled him to obtain a full and accurate history of the patient's antecedents. Too often, in our attempt to learn the family history of any given case, are we met by absolute ignorance on our patient's part of facts concerning even his immediate progenitors, or receive information possessing the authenticity of tradition.

Rarely are we permitted to look back, with reasonably accurate vision, four, five, or even six generations into our patient's past. Cases have, however, been reported of the affection we are considering in which we are afforded such privilege.

Dinkelacker,[1] a pupil of Quincke, wrote a dissertation in 1882 on acute œdema, using as the basis of the essay cases referred to later by Quincke.[2] Among these was a case of a watchmaker, who had for years been afflicted with periodical attacks of acute œdema, whose son, a child of one year, had suffered from his third month with the same affection.

In 1885 Valentin,[3] who had occasion to see this family after the appearance of the papers of these two observers, adds the interesting information that another son, then two years old, not born when the above observations were made, was also afflicted with similar attacks from the first week of life. Another child, a daughter, had shown no sign of the affection up to the time of observation.

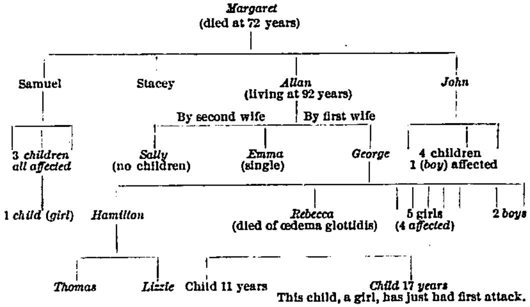
In 1885 Strübing[4] reports a case in a man, aged seventy years, who for forty-five years had had attacks of acute œdema of the face, throat, pharynx, and larynx, the latter so severe that extreme dyspnœa ensued. This would last a few hours and then subside. Between his sixty-third and sixty-eighth year he was entirely free from the throat attacks; then without any evident cause he felt pain on swallowing, with beginning inspiratory dyspnœa. This increased rapidly until in fifteen minutes it had attained such a degree that tracheotomy seemed unavoidable. Respiration was attended with the highest degree of orthopnœa, with action of all the accessory muscles. This condition lasted for a few minutes, then gradually subsided, until six hours later no sign of the distress remained. Now, however, œdema of the face and genitals developed. Four days later all disturbance had disappeared. More frequently than the attacks of œdema have occurred since his twenty-sixth year, at intervals of four to six weeks, attacks of severe vomiting, preceded by a slight sensation of abdominal pain, increasing in intensity up to the culmination in the vomiting. These attacks were attended by marked prostration and followed by sleep, out of which he awoke feeling well. At times the attack was ended in three or four hours, after vomiting four or five times. On other occasions it lasted twenty-four hours, with twenty to thirty repetitions of the emesis.

His sixteen-year-old son suffered from his third year with similar attacks, except that œdema was not so marked a feature. Much more frequent were the attacks of vomiting, in which a large quantity of fluid was ejected. A daughter also suffered from attacks similar to those of her father.

Falcone[5] reports a case of acute recurrent œdema in a child, aged seven years, whose grandfather was afflicted with similar attacks.

Osler,[6] in 1888, reported a case of great interest in which, through the fortuitous recollections of some of the members of the family, and especially the unimpaired memory of a great-grandfather, aged ninety-two years, who had himself been afflicted for seventy-four years, a history of the affection extending through five generations, and involving twenty-two members, was obtained.

The characteristics of the affection in this family noted by Osler were: the occurrence of local swellings in various parts of the body; the almost invariable association of gastrointestinal disturbance, —colic, nausea, vomiting, and sometimes diarrhœa; the strongly marked hereditary disposition:



Krieger[7] cites a case in a man, aged twenty-five years, whose mother was also affected.

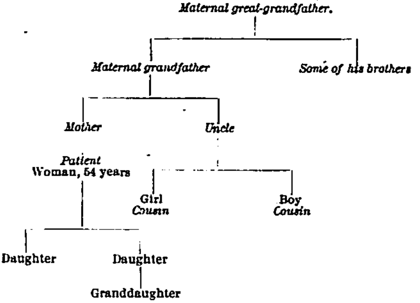
In one of Smith's[8] cases, that of a young woman, subject to recurrent attacks of œdema, the mother was similarly affected.

Fritz[9] gives the history of a man, aged twenty-three years, who fell and struck on the right temple. Shortly after the left eyelid began to swell, until the eye became completely closed. The swelling extended to cheek, lip, and neck. On entrance to the hospital there were cyanosis, dyspnœa, almost entire aphonia, and frothy expectoration. Examination showed the uvula swollen, the left tonsil, the left pillar of fauces, and the left side of the glottis very œdematous. During the night the swelling appeared in the right side of the face, subsiding in the places where it had first made its appearance. On the following day it entirely left the face, but appeared in the right foot and ankle. Lungs and heart normal. Urine 900 c.c., 1022, acid. Urea, 28.8 grams. No albumin or sugar. He was otherwise well and had always been so, except that after drinking on an empty stomach, overeating, or after slight injuries, swelling, usually in extremities and eyelids, would ensue. These attacks had occurred since he was four years old. His paternal grandmother died of œdema of the glottis. One aunt had recurrent attacks of œdema. Two cousins, children of this aunt, died of œdema of the glottis. One of his sisters is also affected with attacks of glottic œdema. Both of his brothers died with the same form of œdema. Eight members in all were affected in this family.

Roy[10] mentions cases of acute circumscribed œdema in a mother and her daughter.

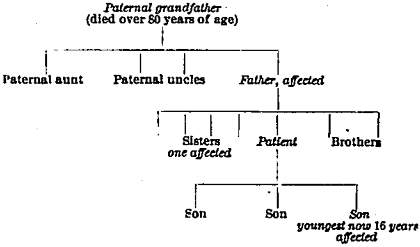
Ricochon[11] reports three generations of acute œdema, accompanied by colic, vomiting, meteorism, fever, and malaise. His cases show a close symptomatic resemblance to the cases of Strübing, already mentioned, and to those of Yarian,[12] which follow. This patient was a woman, aged fifty-four years, who since childhood had acute attacks, commencing with general malaise, followed by swelling of some part of the body, usually the face or extremities, sometimes the shoulders or chest. One or two days later she is taken with very severe sharp pain in the region of the epigastrium, occasionally elsewhere over the abdomen, with marked prostration. This is soon followed by nausea and vomiting, with severe retching. Mental emotion is capable of precipitating an attack with great suddenness.

At times with the œdema, or just as it is subsiding, there have appeared "purple rings" on the chest, neck, arms, and hypogastrium. After free vomiting the pain and œdema disappear, and such an attack in the forenoon does not incapacitate her for work in the afternoon. The attacks appear on an average of every two weeks, nine weeks being the longest period during which she has been free from its occurrence. Her mother had identical attacks from childhood, and died at the age of sixty-three years, "from dropsy." After the menopause she also had attacks of purpura. Her uncle on her mother's side had similar attacks, and died at the age of forty-two years, from œdema of the glottis. This uncle left a child, a girl, who suffers from periodical œdema without the gastralgia and vomiting. A brother of this child, now dead, also had attacks. Her maternal grandfather and some of his brothers had similar attacks, but without the pain and vomiting. Her maternal great-grandfather also suffered with the affliction, but he, too, never had the pain or vomiting. This is as far back as the affection can be traced. Her two children, both girls, while of irritable disposition, never showed signs of her trouble. One died of tuberculosis when twenty-one years of age. The other is living at twenty-five years of age and married. Her grandchild by this daughter has thus far shown no evidence of the affection.



Schlesinger[13] cites an instance in which the affection appeared in four generations. The patient, a man, aged forty-four years, has been subject for twenty-two years to the following attacks:

Commencing with a subjective feeling of irritation or depression, an exanthem appears on some part of the body. After six or eight hours this disappears, then on some portion of the body a rapidly developing swelling occurs, usually attended by pain in the epigastrium. This swelling develops with great rapidity, reaching its maximum in a few moments, lasts from one to three days, and then disappears. In the earlier years it occurred every half-year, later on at intervals of every ten or eleven days.



T. Wardrop Griffith,[14] of Leeds, reports a case of an adult woman, aged twenty-three years, who from infancy had been subject to attacks of localized œdema involving the hands, feet, shoulders, genitals, and throat. At the age of twenty-three years death occurred suddenly from laryngeal obstruction. Her father had been subject to similar attacks from earliest infancy. At the age of twenty-one years he had a laryngeal attack; a few years later another; and at the age of twenty-nine years a third attack caused his death. Examination of the larynx of the woman showed, in cross-sections, that the œdema involved not merely the mucous membrane, but also the deeper connective tissue, and even the substance of the muscles themselves, which condition Griffith thinks would prevent the abductors from enlarging the aperture during inspiration, and so lead to death.

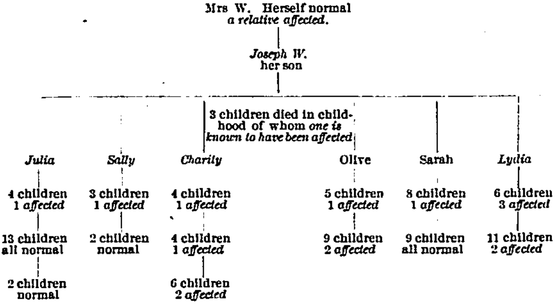
These instances leave no doubt of the influence of heredity in some of these cases of acute œdema. The characteristics of this affection are recurrent attacks of acute œdema in varying portions of the body, usually of rapid development and brief duration, and often associated with disturbances of the gastrointestinal tract.

We now come to the consideration of a form of œdema with quite different characteristics. This variety is as slow in its development and as sluggish in its course as the form we have just described is acute and transient.

Higier[15] says, in speaking of œdema not of organic origin, but occurring in connection with some neurotic condition: "It may appear and disappear in some hours or some days, but it may also last the life long. It is not rarely hereditary." This would seem to indicate that this author regards these two forms as in close relationship. It is questionable, however, whether we are justified in so considering them, on the basis of their clinical characteristics.

Heredity is as strongly indicated in some of these chronic cases as in the above-cited acute forms. The features peculiar to this chronic form of œdema are swelling in one or more extremities or parts of an extremity, of gradual onset, and usually life-long course, unattended by pain or disturbance of the general health. Some slight exceptions to this definition may be found in individual cases; such as transient pain, or the presence of some coincident affection, usually of the nervous system; but they are so seldom as to but emphasize the rule.

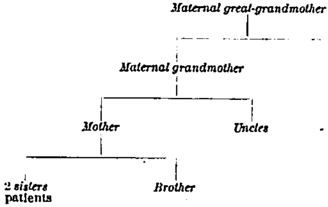
The following remarkable cases are reported by Milroy:[16]



Of six generations, comprising ninety-seven individuals, over 22 per cent. were affected. In the third generation there were nine individuals, all children of one father. Of these, three died in childhood of unknown cause. Of the remaining six, four lived to be over seventy years of age, and two were eighty and eighty-two years, respectively, at time of death. The other two died at the ages of sixty-six and thirty-eight years. This indicates in a striking way how absolutely harmless this form of œdema appears to be. We shall see that it is, in this respect, in sharp contrast to the form we have previously considered.

Jopson[17] reports two cases of marked subcutaneous œdema of the lower extremities of congenital origin in children, aged four years and one and one-half years, respectively, whose father, during his childhood, had a similar condition, which disappeared as he became older. The swelling in both cases pitted on pressure. In the older child the foreskin at birth was also involved.

In 1899 Meige[18] reported cases of a similar affection occurring in eight members of one family through four generations. The reader is referred to his excellent article for photographs of the condition.



In each of these cases the swelling came on at the period of puberty or slightly later, that is, from the thirteenth to the twenty-third year, and continued a chronic course, involving in some cases only one leg, in others both legs, in others both leg and thigh.

Desnos,[19] in speaking of chronic œdema, mentions that it may be hereditary, and thinks that when it is so it is usually down the maternal line. These cases of Meige, published eight years after this statement was made, seem to confirm the opinion. So few have been the cases reported, however, of this chronic hereditary œdema that it is impossible to determine that such is the case. It certainly is not so in acute œdema of hereditary nature.

In the cases reported by Dinkelacker, Quincke, and Valentin, and in the instances cited by Strübing, it was transmitted from a father to a son.

In Osler's cases this repeatedly occurs. In one instance the disposition can be traced through the male line for four generations;

great-grandfather, grandfather, father, and son each being subject to the attacks. This is strikingly exemplified in Schlesinger's cases, where also four generations in the paternal succession were affected. In Yarian's patient the maternal element is somewhat more evident, but even here we see that among her ancestors and relatives a father transmitted the disposition to several of his sons, and through one of these, not alone to a granddaughter, but to a grandson and great-grandson.

There have been many endeavors to solve the problem of the production of œdema. One of the earliest attempts at the solution of the question was that of Lower,[20] in 1669. Lower ligatured the inferior cava and claimed to have thereby obtained œdema of the lower extremities and ascites, as the result of the venous stasis, the blood serum passing through the vessel walls as through a filter. This was the mechanical filtration theory. Wherein the error in his experiment lay does not now appear. At all events, this was the prevailing view for two hundred years up to 1869.

Virchow,[21] in his *Handbook of Special Pathology and Therapy*, published in 1854, says: "I have never been able to convince myself that in mechanical dropsy the fluid passes through the walls of the veins. The location of the transudation is mainly the capillaries. With a certain degree of lateral pressure the capillary wall may be permeable for watery fluid."

This is a practical acceptance of the mechanical filtration theory for certain forms of œdema, but he says further: "Exceedingly difficult is finally the question of the primary essential or idiopathic, and the secondary, consecutive, or symptomatic dropsies. One may assume that these primary and essential dropsies are brought about by an arterial fluxion in parts whose blood and lymph vessels are in a state of disturbed nutrition."

In 1869 Ranvier[22] took up Lower's experiments and utterly failed to obtain œdema in that way. All the signs of venous stasis appeared, but œdema was not one of them. When, however, he cut the sciatic nerve on one side, on that side he obtained œdema, while on the other side no transudation from the vessels occurred. To the writer the most interesting result of Ranvier's experiments is the following: Œdema was only obtained when the sciatic nerve itself, outside of the spinal canal, was cut. When its roots of origin inside the canal before the accession of many sympathetic fibres were severed no dropsy resulted.

In 1877 Cohnheim and Lichtheim[23] published the results of numerous experiments. They concluded that a hydræmic condition of the blood in itself alone cannot cause œdema. For its production there must exist coincidently some injury to the vessel walls. They show that transfusion of salt solution, even to the extent of 64 per cent. of a dog's weight, is not followed by œdema of the skin. Such injury to the vessel walls may, however, be brought about in time by a hydræmic condition itself. "The normal function of the vessel walls is dependent upon the continuation of normal circulation in the vessels. . . . It is hardly to be doubted that not alone the oxygen, but other constituents of the blood are equally important factors for the maintenance of the normal function of the vessels."

Sotnischewsky[24] thought that œdema could be produced by simple constriction of the veins, provided the total venous outflow of the limb was cut off, while every opportunity for the afflux of blood to the part was afforded. He found, however, that when he also cut the nerve supplying a vein, œdema occurred, even if the total venous outflow was not restricted.

Cohnheim[25] again, in 1882, emphasizes the greater facility with which œdema occurs in hydræmia from the poorly nourished and permeable vessels. He cites the experiment of Ostroumoff, in the course of his remarks. Ostroumoff irritated the peripheral end of cut lingual nerve with an induced current of gradually increasing intensity. He obtained a primary hyperæmia, followed in ten minutes by œdema, which, ten minutes later, had reached marked proportions. In 1884 some exceedingly interesting experiments were carried out by Landerer[26] to determine the part played by the elastic tissue in transudation. He found tissues subject to dropsy markedly deficient in elasticity, and concluded that this factor was one of great influence on the circulation of the blood and lymph. He considers œdema and inflammation also, an impairment of "the elastic equilibrium of the circulating fluids of the body." This subject was mentioned by Monro previous to 1777, for in the German translation of his work on dropsy of that date, on page 11, is the following: "Es giebt viele und mancherlei Ursachen von der Wassersucht. Die vornehmsten davon sind folgende. . . . Eine Erschlappung und Schwäche der Fasern. Diese Ursache fällt öfters vor."[27]

Gaertner,[28] repeating the experiments of Cohnheim and Lichtheim, thought that their injection of the salt solution was too rapid, and that œdema ensued when the fluid was more slowly introduced.

Gergens[29] found that in frogs the vessels allowed much more fluid to pass through when the medulla was destroyed.

Of much interest are the experiments of Salvioli.[30] He found that an excess of artificial hydræmia did not cause transudation into the subcutaneous tissue, but did to a certain extent produce œdema of some of the internal organs. When, however, he ligatured the renal and inferior mesenteric vessels, fluid did collect in the subdermal spaces of the abdomen, thorax, and thighs. From this he concluded that some vessels are naturally more permeable than others, and that when these vessels are cut off from the circulation, in this state of artificial hydræmia, those next in order of permeability permit transudation to take place. He regards the different organs as possessing different degrees of permeability, and thinks that the location of such transudation may be varied by suppressing the vessels that under usual conditions most readily allow filtration.

Jankowski[31] says that œdema from hydræmia in itself alone does not exist, but that in such condition where the vessel walls are injured even slight disturbances of circulation suffice to produce transudation.

Recklinghausen[32] considered œdema the product of increased filtration of blood plasma, dependent on abnormal pressure in blood- and lymph-vessels or on chemical change in the blood plasma.

Heidenhain[33] and, at about the same time, Hamburger,[34] of Utrecht, advanced the theory that the capillary endothelium possesses powers of secretion, and is not merely a filtering agent.

Horsley and Boyce[35] saw the results of Ranvier's experiments confirmed in nine out of twelve cases, and, in an enumeration of the various factors in the production of œdema, quote the paper of Tigerstedt and Santesson[36] (which was not available to me) as disposing once and for all of physical theories, and of the dependence of transudation on mere variation in pressure on the two sides of a permeable membrane.

Hamburger,[37] in a paper on the regulation of the "osmotic tension" of fluids in the peritoneal and pericardial cavities, considers as factors in transudation, venous hyperæmia, increased permeability of vessel walls, and irritation of the capillary endothelium by some substance produced by disease, and later adds,[38] as a fourth factor, "retardation of absorption."

Lazarus-Barlow,[39] in a most valuable contribution to the subject, concludes that œdema is not caused by merely mechanical means, even in the cardiac variety; that there is no evidence of any damage to the bloodvessels, other than that caused by starvation of the same; and that anæmia, being in fact a starvation, in conjunction with non-removal of waste products, is an important cause of œdema.

The non-removal of waste products introduces the element of poisoning, which, he thinks, is a more important factor than mere anæmia.

Senator[40] believes that dropsy does not necessarily depend on disease of the kidneys, but upon a coincident injury to and consequent increased permeability of the blood- and lymph-vessels of the skin, and of the serous and mucous membranes.

Boddaert[41] says: "It is the general scientific opinion that obstruction of the lymphatics plays no part in the development of œdema by constriction," but concludes from his researches that œdema by constriction *is*, at first, at least, essentially lymphatic.

He considers, as a result of direct experiment, that the œdema produced in one extremity by ligature of the lymphatics alone is identical in kind with that produced in the other limb by constriction of its entire circumference (in the upper part of the thigh). His researches were conducted on rabbits.

Opitz[42] presented, in 1899, an excellent general consideration of the whole subject of œdema.

He thinks that the filtration theory received a hard blow from the experiments of Cohnheim and Lichtheim, whose work he considers the starting-point for the modern theory of œdema.

Howell[43] classes œdema as follows: Œdema of engorgement, œdema of inflammatory origin, that of hydræmic or cachectic nature, and that of angioneurotic character. Changes in the vessel walls of nutritive character, qualitative changes in the blood and toxæmias resulting in malnutrition and nerve irritation, are all causative factors. Instances of such blood conditions are seen in anæmia, chlorosis, scurvy, slow starvation, chronic discharges, etc., and all debilitating influences resulting in hydræmia.

Funck,[44] in an exceedingly interesting paper on the physiology and pathology of dropsy, says that it has been experimentally shown that, within moderate limits, as in ordinary disease, neither a diminution of albumin nor an excess of water in the blood is sufficient to cause œdema. To produce œdema, something more is required than more facility of filtration of watery blood, in fact, malnutrition of the vessel wall, lessened elasticity from vasomotor paralysis, rendering the vessels more permeable for fluid.

Albu[45] believes that a watery condition of the blood, with loss of albumin, favors the transudation of serum from the vessels; that a "hydræmic plethora," with lessened outflow of fluid, tends to the same condition; while the *sine qua non* is an increased permeability of the vessel walls. These three theories are practically those of Bright, Bartels, and Cohnheim, respectively, combined.

Among the latest works on the causation of œdema known to the writer, and which practically brings the subject up to date, is the interesting work of Jacques Loeb,[46] of Chicago. Loeb considers the filtration theory utterly erroneous. He says: "I consider that the power for the movement of fluid in the tissues in cases of œdema (as in all other cases) is essentially to be sought for in osmotic force, and that the œdematous conditions, that is to say, the penetration of fluids into the tissues, occur when the osmotic force in the tissues is higher than that of the blood and lymph. In other words, the œdema must have as its basis such causes as raise the osmotic force of the tissue or lessen the osmotic force of the blood and lymph." This may be a change in the tissues of chemical nature that increases its osmotic force. Loeb produced such a change in a muscle by totally shutting off its circulation, and suggests that it may have been due to lack of oxygen. He shows that the osmotic pressure may be 300 times the degree of intravascular pressure that has been thought sufficient to produce the highest degree of œdema of the lungs.

Many experiments with frogs showed that a given muscle in a limb, when the circulation to the limb was totally restricted, absorbed fluid to from 1 per cent. to 3 per cent. of its weight in eighteen hours, 15 per cent. in forty-eight hours, 25 per cent. to 40 per cent. in seven days. A similar result ensued when the muscle was removed and placed in salt solution.

This chemical change in the muscle, which increases its osmotic force, and is apparently due, he thinks, to lack of oxygen, is accompanied by acid formation. Osmotic force may be increased in the tissues by alkalies, acids, and loss of water.

"The occurrence of œdema is brought about by chemical changes in the tissues. These chemical changes influence first the osmotic force in the sense that in the tissues that are œdematous it is higher than in the blood and lymph. Second, these chemical changes may also bring about morphological changes."

As Sewall[47] pointed out some years ago, there can be no question but that osmosis in living animal tissue is a different problem than it is in dead membrane. The endothelial walls of the capillaries are composed of living cells engaged in active vital process, vital, at least, as regards their own existence, if in no other way. That this living cell membrane allows the fluid of the blood or tissues to pass through it, subject only to the law of diffusion, as applicable to dead inert membrane, seems to the writer extremely problematical, although, perhaps, possible. Another source of error is the assumption that deductions drawn from experiments on lower animals are, without further qualification, applicable to physiological or pathological processes in the human being.

Not alone do different animals vary greatly in the degree to which a physiological or pathological process may be carried out, but also corresponding organs in the different species may possess functions differing greatly in degree, if not in kind. This is, perhaps, nowhere more evident than in the cutaneous covering of the various animals. Thus the skin of man is an organ of excretion of the utmost importance, while in the dog this is, by comparison, a function of infinitely less value. In the rabbit and guinea-pig such is also the case, while in some animals scarcely any analogy exists. The dog, and occasionally the rabbit, have, as a rule, been the animals employed in the attempt to solve this question. It would seem that such marked variation in the function of an organ, in man of the greatest importance, in the animals experimented upon of relatively little importance, in the elimination or retention of the watery constituents of the body, must have its influence on the results of these experiments, and should be considered in the deductions drawn therefrom for application to similar processes in the human being.

However, the actual process of transudation may take place, we know, beyond all reasonable doubt, that the *exciting* factor in this process may be, in numerous cases, of neurotic nature. It is not necessary to go beyond the limits of the human species to find convincing evidence of this fact.

The occurrence of œdema in traumatic or surgical injury to a nerve or in other nerve disturbance has frequently been seen.

The œdema following nerve section; the transudation occurring in the area of distribution of a nerve which has been the seat of neuralgic pain; the œdema occasionally met with in neuritis; that of paralyses, and that sometimes seen in tetany are all instances in which the neurotic factor is apparently direct. Further evidence is found in the occasional occurrence of not only a circumscribed but a unilateral œdema, of which a case will be noted among these here reported. (Fritz.) These cases are somewhat analogous to those of unilateral hyperhidrosis or hemidiaphoresis sometimes seen. The occurrence, simultaneous with the transudation, of symptoms of undoubted nervous origin, or the occurrence of the same at other times, or occasionally in alternation with the œdema, furnishes also strong presumptive evidence of its neurotic character. The extremely rapid onset, development, and disappearance of the acute attacks can hardly be accounted for on any other than a neurotic basis.

Finally, the heredity itself in the cases above mentioned strongly suggests a neurosis.

Of interest in this connection are the cases of periodical vomiting described by Leyden,[18] who cites their analogy to the "gastric crises" of Charcot. These attacks closely resemble those of Strübing's and Yarian's cases, apart from the œdema. They were, as in the case of Strübing's younger patient, accompanied by the vomiting of large amounts of watery fluid. In none of these cases did œdema ever appear, but the gastric symptoms are practically identical with those seen so frequently in these cases of acute œdema.

The neurotic element in the chronic cases is not evident, although Meige is inclined to consider them analogous to the trophic disturbances seen in lesions of the cord.

No more curiously interesting affection exists than this recurrent acute œdema. Here we have in one family a man living in unimpaired vigor of mind and body at ninety-two years, having suffered with the affection for seventy-four years, while in his family a child died of the affliction in early life, and an adult woman forfeited her life to the same disease. That death may be narrowly escaped is illustrated by the fact that his mother at one time nearly died of "shortness of breath," but, nevertheless, lived to be seventy-two years old.

That death may come with great suddenness and without warning is shown by Griffith's case. This woman was playing on the floor with her baby, apparently in perfect health, when she was seen to suddenly put her hand to her throat as if she felt trouble there and immediately fell over dead.

This affection has occasionally been regarded as one of little seriousness to life. It is, however, a condition of serious import, and, once occurring, renders the patient's future always insecure.

Krieger's case was found dead in bed, and autopsy showed that death was due to œdema glottidis. Five of the eight members of the family cited by Fritz died of glottic œdema, including both of the patient's brothers.

Griffith's case died at twenty-three years and her father at twenty-nine years, both of œdema of the glottis.

These cases are only those occurring in the families where the affection manifested some hereditary tendency. Many fatal cases have been recorded in instances of acute recurrent œdema where heredity was not manifested, and which, therefore, are not included among those we are considering. But if we consider the mortality in these hereditary cases alone, we shall see that the affection shows a death rate of about 16 per cent.; while of the remaining cases, 6 per cent. had had attacks in which death was imminent.

This is a mortality in strong contrast to the prognosis given by some writers for acute recurrent œdema; and it will at once be evident why this is so, when we consider that cases of this affection are rarely under the observation of any one observer for any prolonged period of time.

The full life history of the individual is, therefore, not obtained.

In a somewhat extensive review of the general subject of acute œdema previous to the study of the hereditary cases, it was evident to the writer that the mortality was much greater than was generally considered, but no conception of as high rate as the above percentage indicates was obtained. It would seem, however, that we must be nearer the truth in deduction based on these hereditary instances, for here we know the life history of many of the individuals, and further knowledge of the ultimate fate of those still living would tend not to diminish but to rather increase the death rate.

In the fatal cases death was due, almost without exception, to œdema of the glottis.

If in the adult death may occur with the extreme suddenness seen in so many of these instances from obstructive œdema of the throat, it might well be thought that in the child this would be much more likely to occur.

Curiously enough, however, the majority of the deaths in the cases here reported occurred in adult life, notwithstanding the fact that many of the individuals had been afflicted with the affection in childhood.

Another singular fact is that while in almost every family there were many cases that began in childhood, there were a number in which the affection did not appear until after this period; and in one family, in four generations, no case occurred until adult life was attained.

Direct exciting cause seems often to be present in the individual attacks. In a number of instances trauma appeared responsible for the onset; in others exposure to extremes of temperature or emotional excitement were apparent factors. These can but be regarded as merely the sparks that induce the explosion of nerve force, already in a state of hereditary unstable equilibrium.

Of the ultimate neurotic nature of the affection, it would seem that there could be no serious doubt.

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